



Armed Forces College of Medicine

AFCM



Steroid hormones synthesis

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

- Discuss different types of steroid hormones regarding sites of synthesis , secretion, transport and biological effects
- Illustrate steps of different pathways of biosynthesis of steroid hormones
- Determine the mechanism of action of steroid hormones
- Outline the synthesis of steroid hormones in testes and ovary
- Discuss Congenital adrenal hyperplasia and polycystic ovary



Lecture outlines

Types of steroids

Steroid hormones Synthesis

Steroid hormone synthesis in adrenal cortex:

Synthesis of the

= Glucocorticoids
(e.g :cortisol),

=Mineralocorticoids
(e.g : aldosterone)

=Adrenal androgen

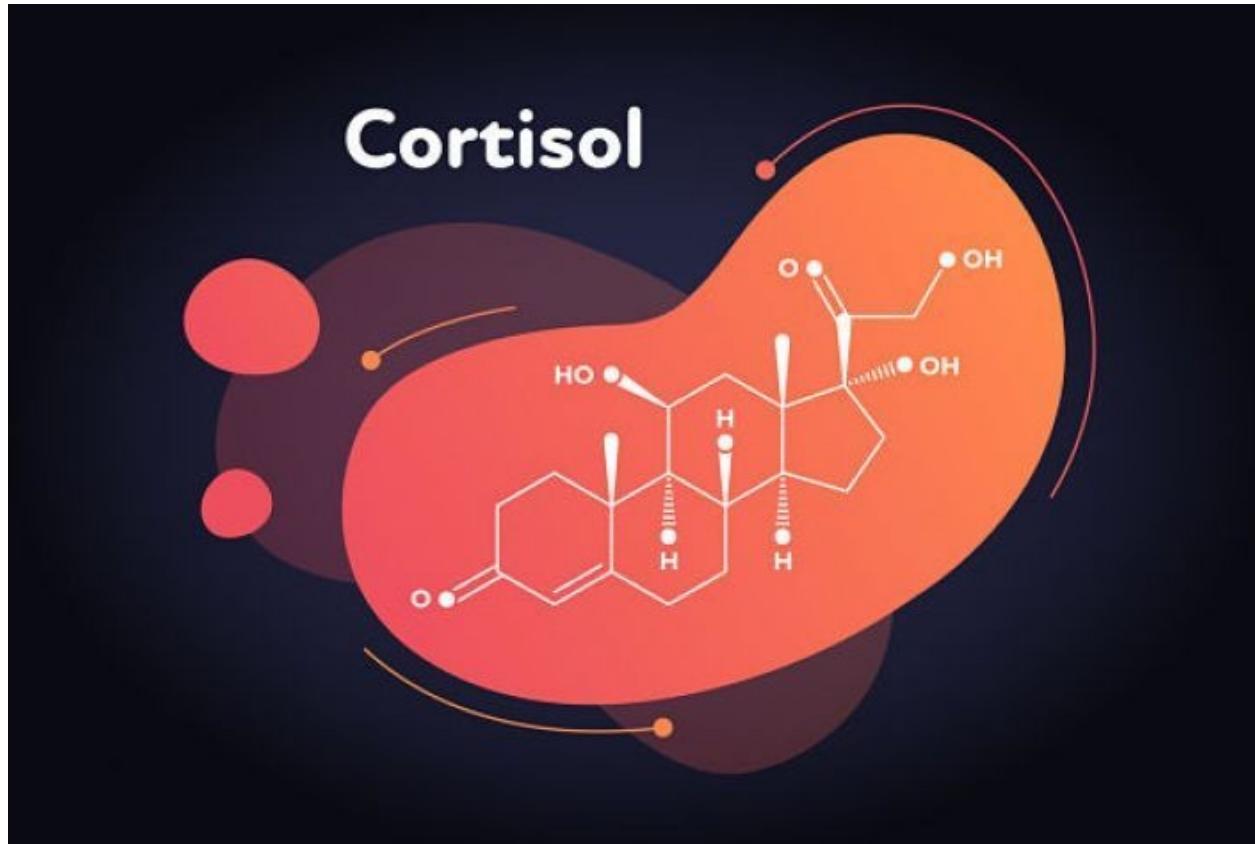
Steroid hormones Synthesis

Synthesis of steroid hormones from gonads

Clinical importance

1-Congenital adrenal hyperplasias (CAH)

2-Polycystic ovary syndrome

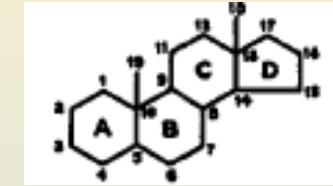


- **Types of steroids**

Steroid Hormones

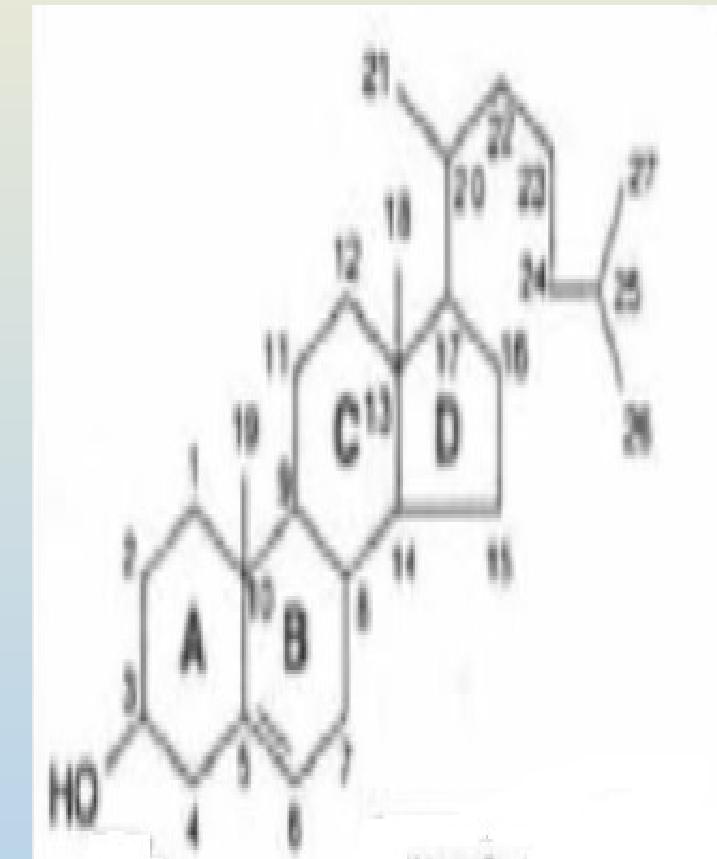


Are group of hormones that belong to the class of chemical compounds known as **steroids**



Types of steroids are:

1. Cholesterol (animal origin) :
2. Ergosterol (plant origin).
3. Vitamin D group (D₂ and D₃).
4. Bile salts.
5. **Steroid hormones**
 - a) Male sex hormones. b) Female sex hormones
 - c) Adrenocortical hormones

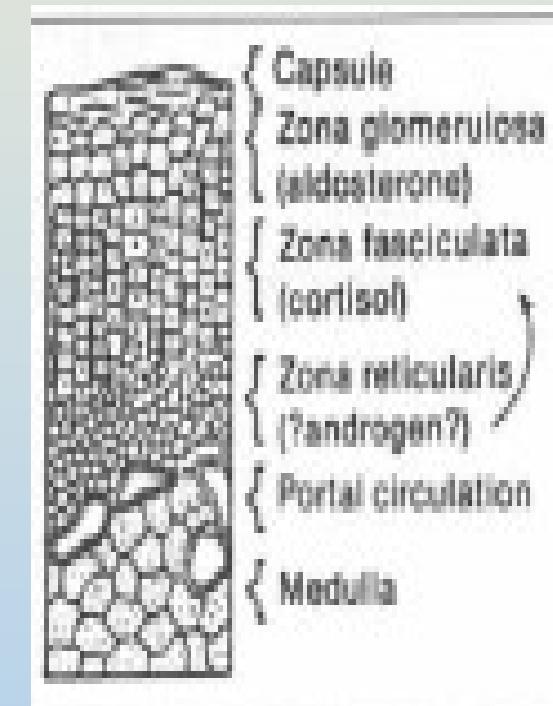
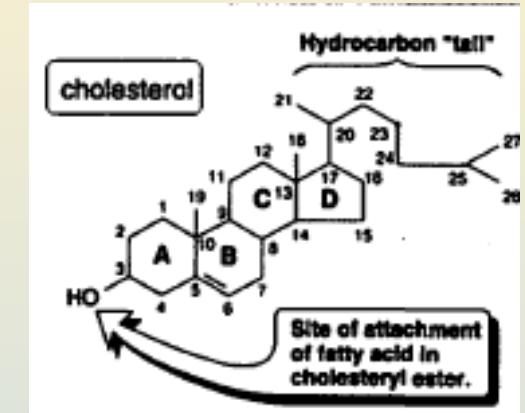


Steroid Hormones



All steroid hormones are derived from **cholesterol**

- They are secreted by the **adrenal cortex**, **testes**, and **ovaries** and during pregnancy by the **placenta**
 - **& Some peripheral tissues**
(as adipose tissue & the brain)
- They are transported through the **blood** to their target organs where they perform different physiological functions



Classes of steroid hormones



Corticosteroid s

1-Glucocorticoids e.g
Cortisol

2-Mineralocorticoids e.g
Aldosterone

Remember

Glucocorticoids: Adrenocorticotrophic hormone (**ACTH**) stimulates its **synthesis & secretion.**

Mineralocorticoids: Its production is induced by **Angiotensin II & decrease in Na/K ratio.**

SEX Hormones production is regulated by LH & FSH



QUIZ

- **Steroids have**
 - a) Sterol nucleus with two alkyl chain attached to the ring D of cholesterol
 - b) Sterol nucleus with two CH3 between C and D ring and A and B ring of cholesterol
 - c) Sterol nucleus without CH3 between C ring and D ring of cholesterol
 - d) Sterol nucleus but lack the alkyl chain attached to the ring D of cholesterol
- **specific cortisol binding protein, transcortin is a**
- **(A) Albumin (B) α 1-Globulin**
- **(C) α 2-Globulin (D) β -Globulin**

Steroid hormones Synthesis

Steroid hormone synthesis in adrenal cortex:

Synthesis of the

- *Glucocorticoids (e.g. :Cortisol),**
- *Mineralocorticoids (e.g. : Aldosterone)**
- *Adrenal androgen**

Synthesis of steroid hormones from gonads

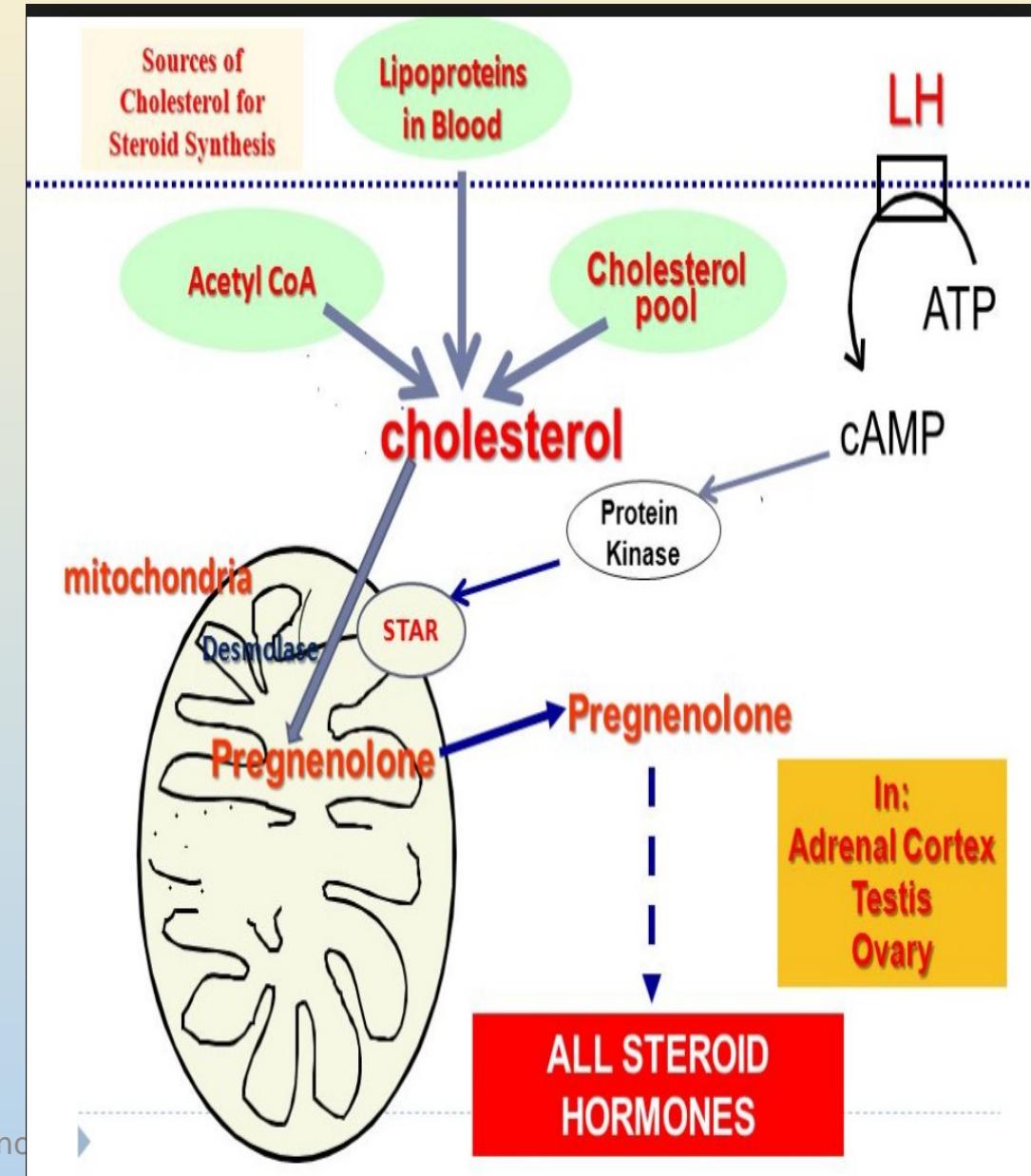
Steroid hormones Synthesis



- **Cholesterol is the precursor of all classes of steroid hormones**
- **There is a common metabolic pathway for the biosynthesis of all steroid hormones.**
- **A series of enzymatic steps in the mitochondria & ER of steroidogenic tissues convert cholesterol into steroid hormones.**
- **The first step is the conversion of cholesterol Into pregnenolone.**
- **This reaction is the rate limiting step in steroidogenesis and occurs in the mitochondria.**
- **This reaction activated by ACTH**

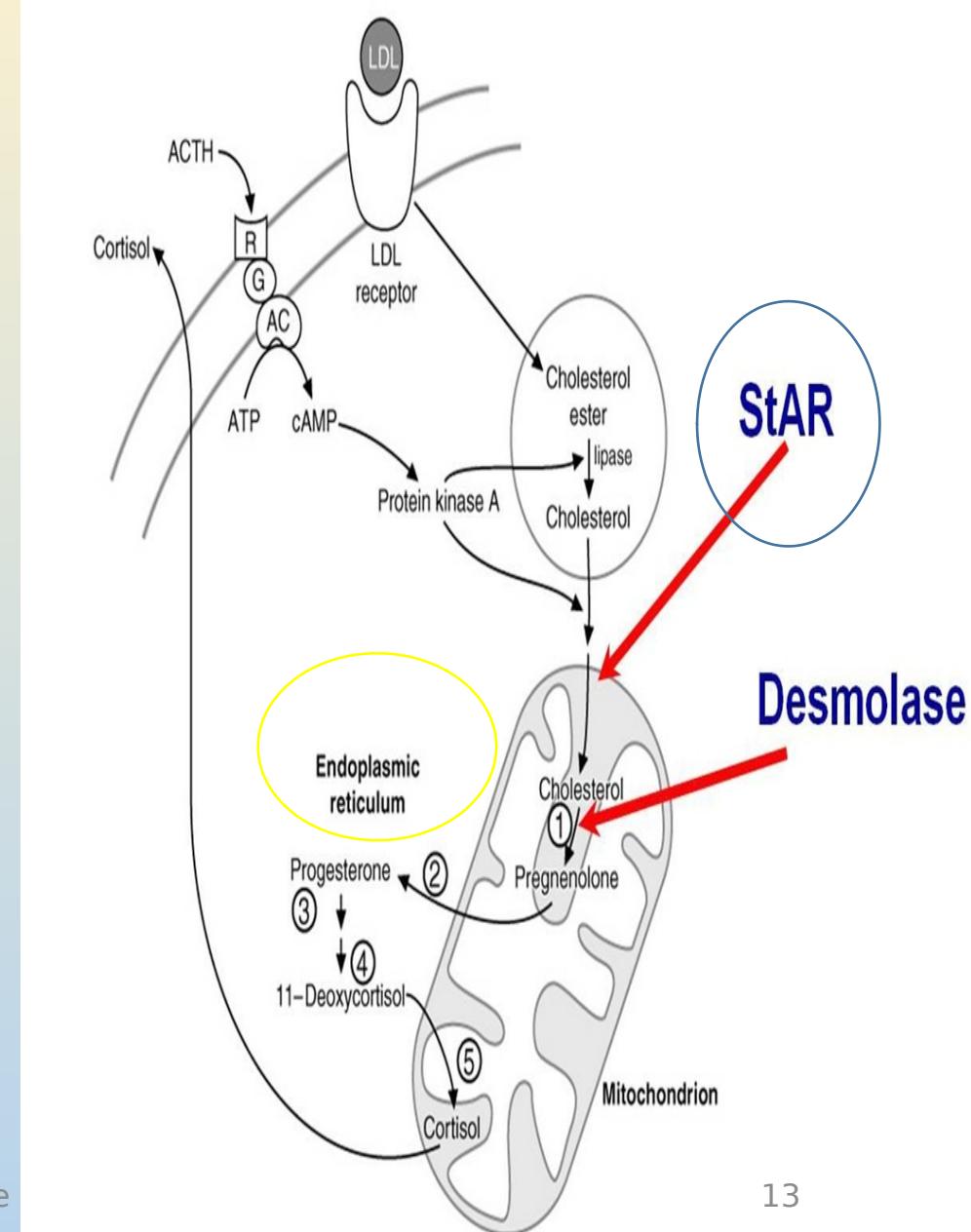
❖ The cholesterol substrate can be :

- 1-Newly synthesized,
- 2- Taken up from lipoproteins,
- 3-Released by an esterase from cholestryl esters stored in the cytosol of steroidogenic tissues.
- The cholesterol moves to the outer mitochondrial membrane. An important control point is the subsequent movement from the outer to the inner mitochondrial membrane.





- The cholesterol moves to the outer mitochondrial membrane.
- An important **control point** in the synthesis of steroid hormones is the **movement of cholesterol** from the outer mitochondrial membrane to the inner mitochondrial membrane.
- This process is mediated by **StAR** (**steroidogenic acute regulatory protein.**)





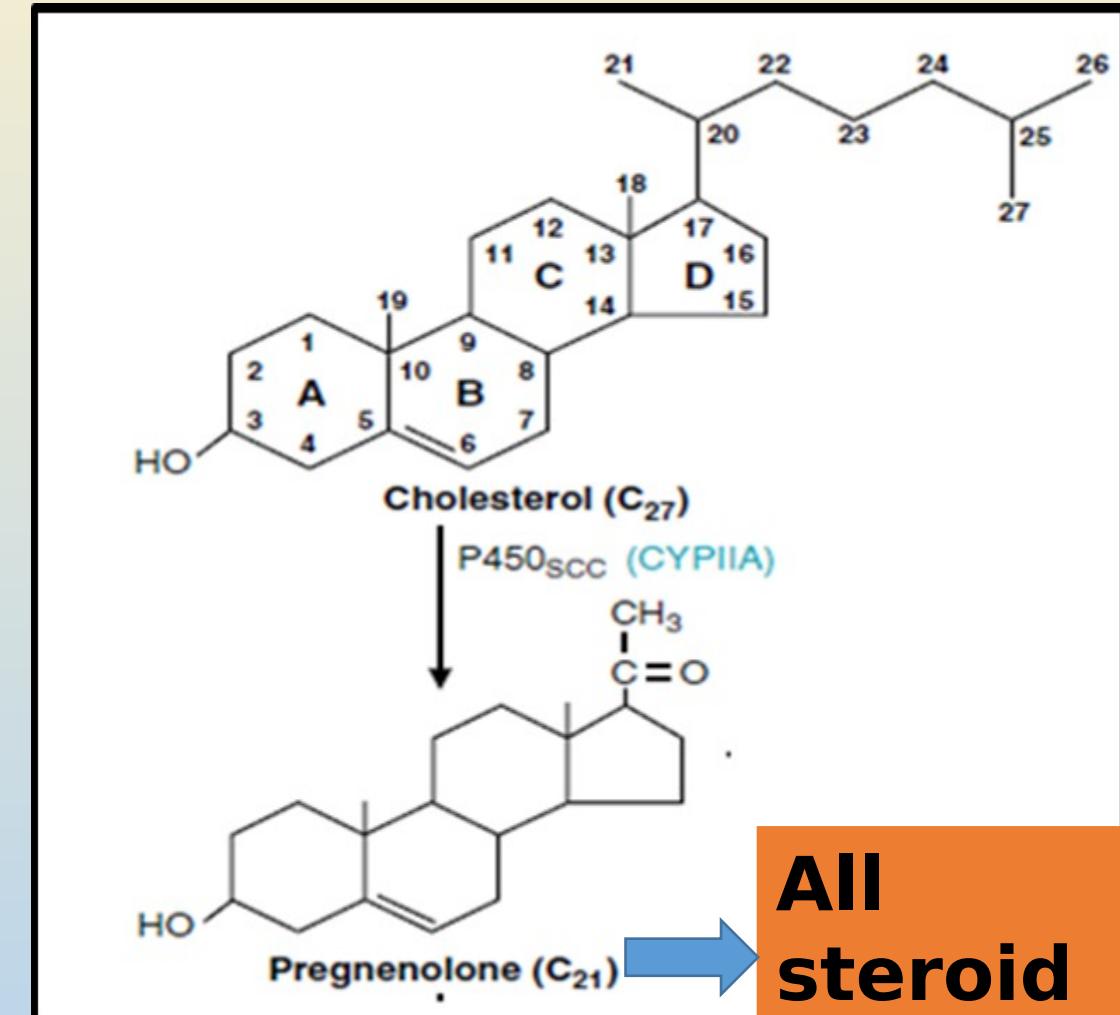
1- Steroid hormone synthesis in adrenal cortex:

**Glucocorticoids (e.g :cortisol),
Mineralocorticoids (e.g :
aldosterone)
Adrenal androgens**

First Step



- The **initial** and **rate-limiting** reaction converts **cholesterol** to the **21-carbon pregnenolone**.
- **Pregnenolone is the parent compound for all steroid hormones.**
- This step occurs also in **ovary, and testis**.



All
steroid
s

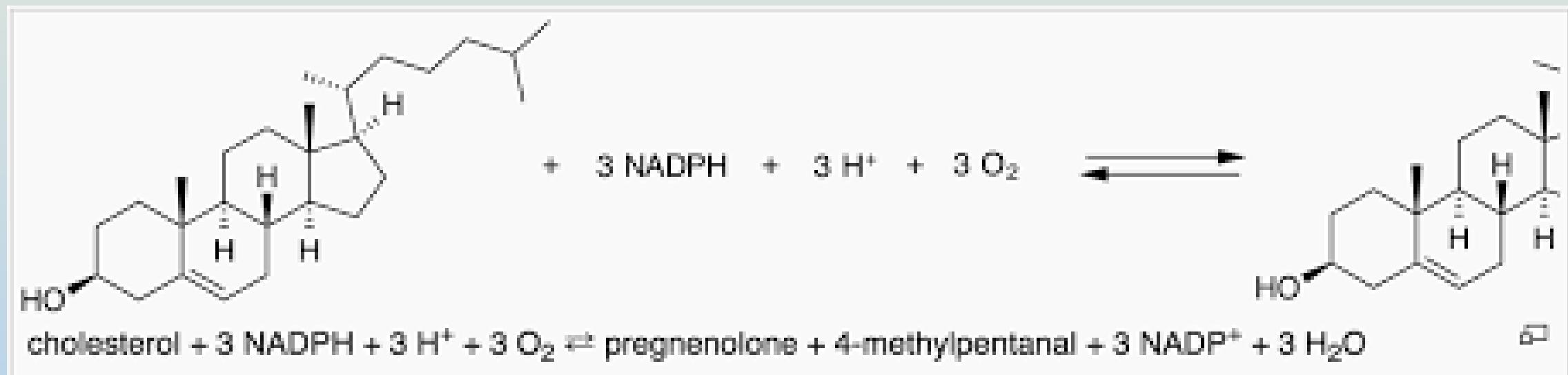
First Step



- Is catalyzed by the cholesterol **side-chain cleavage enzyme**

(A cytochrome P450 mixed function oxidase of the inner mitochondrial membrane)

- NADPH** and **molecular oxygen** are required for the reaction





Note: Pregnenolone is oxidized

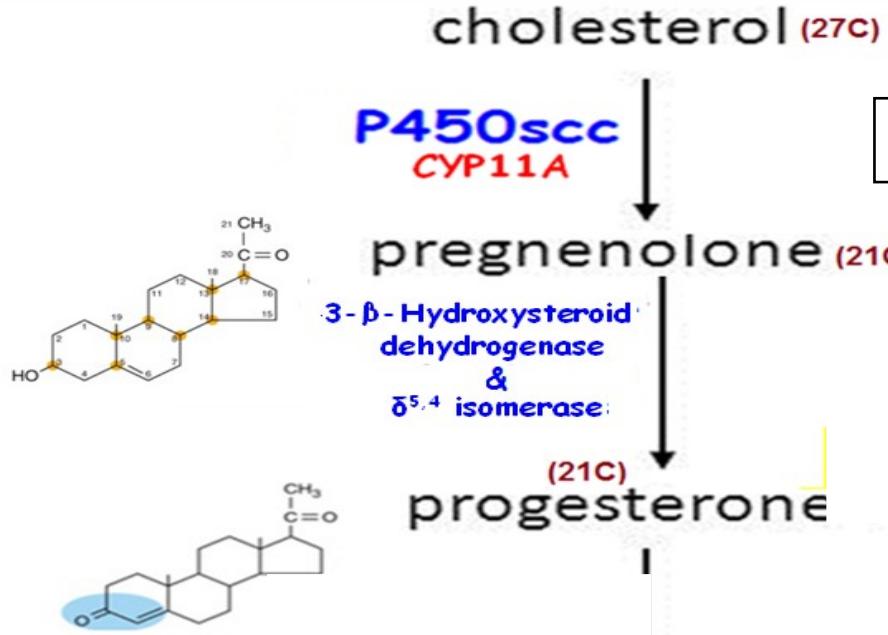
and then isomerized to

progesterone which is further

modified to the corticosteroid

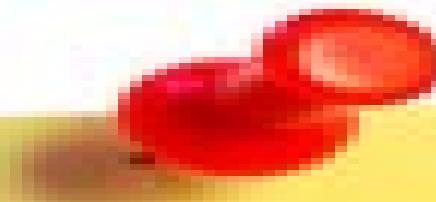
hormones by hydroxylation

reactions that occur in the ER



Synthesis of Cortisol and Aldosterone

CYP = Cytochrome P450

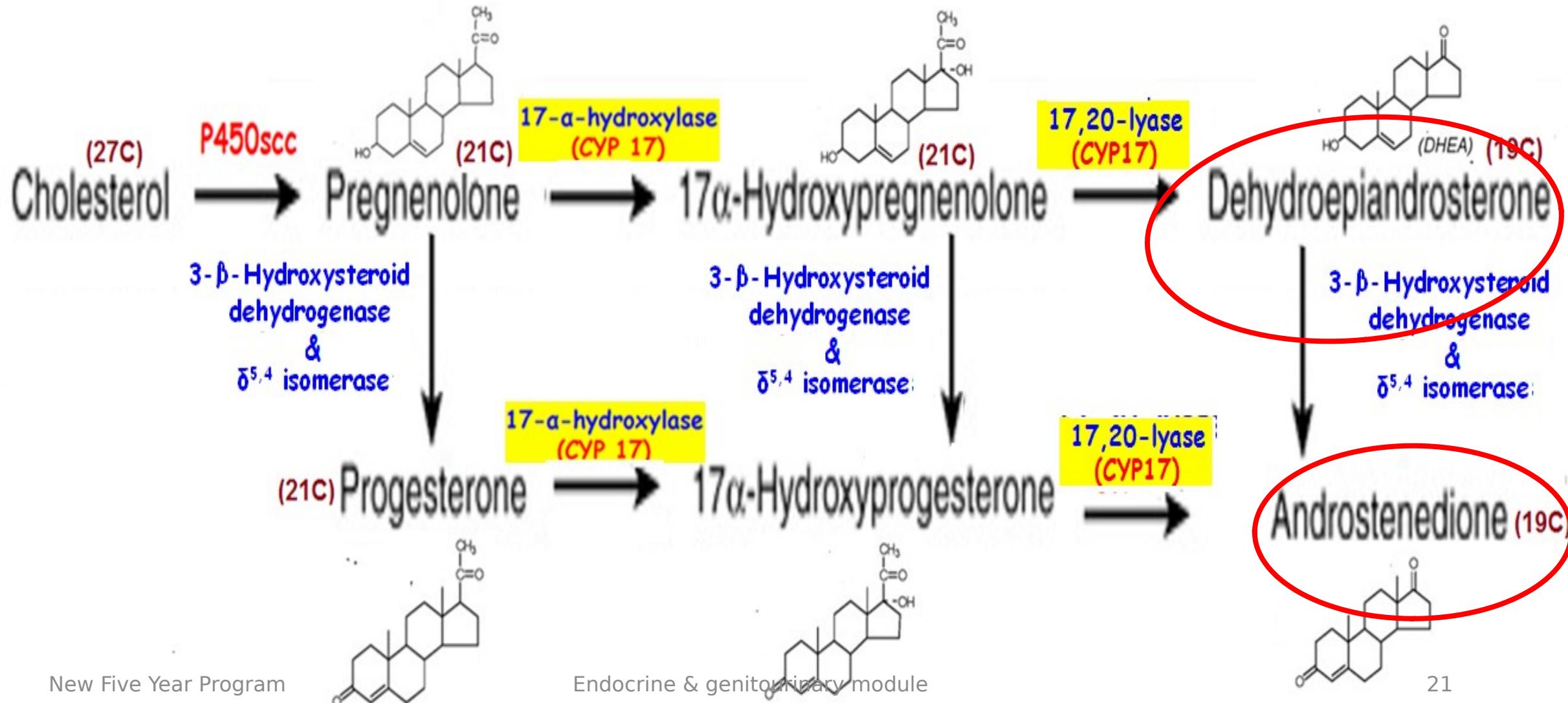


Note: 3- β -Hydroxysteroid dehydrogenase and δ 5,4 isomerase are the **only enzymes in the adrenal pathway of corticosteroid synthesis that are **not members** of the cytochrome P450 family**

Synthesis of the Adrenal Androgens:

- Dehydroepiandrosterone (**DHEA**) & **Androstenedione**)
 - Both the inner (**zona reticularis**) & middle layers of adrenal cortex produce **androgens**

Synthesis of the Adrenal Androgens:





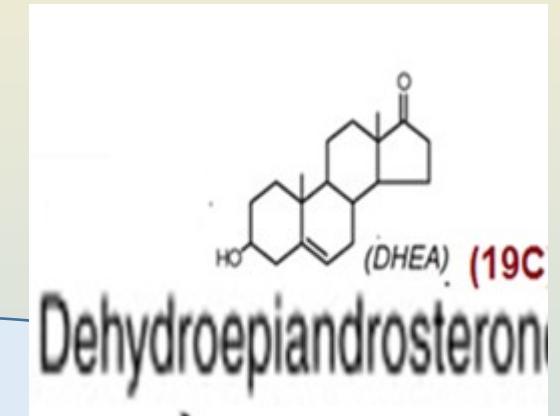
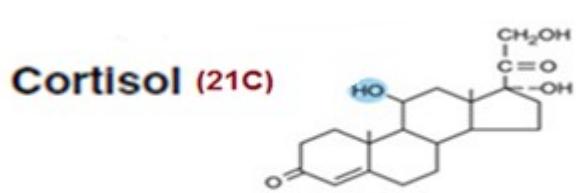
Note: Although adrenal androgens themselves are weak they are converted in peripheral tissues to testosterone a stronger androgen & to Estrogens.



**Note: CYP17 is bifunctional enzyme
has both 17- α -hydroxylase activity &
17,20-lyase activity.**



Glucocorticoids and mineralocorticoids contain 21 carbon atoms and have 2 carbon side chain at C-17.



Androgens contain 19 carbon atoms and have keto or hydroxyl group at C-17.

2- Synthesis of steroid hormones from gonads :

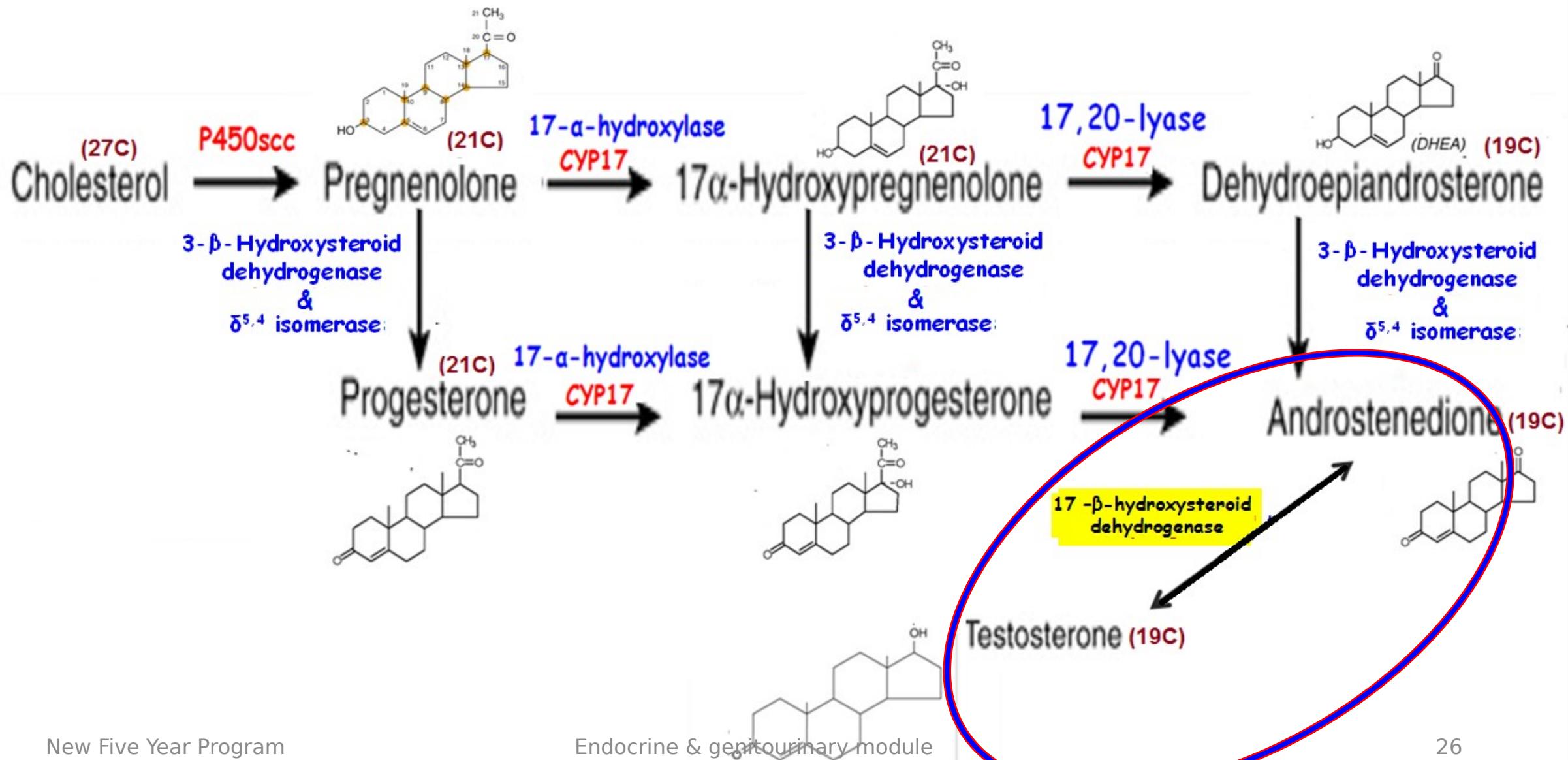
The testes and ovaries synthesize hormones necessary for sexual differentiation and reproduction

The gonads have 2 functions which are production of germ cells and sex hormones.

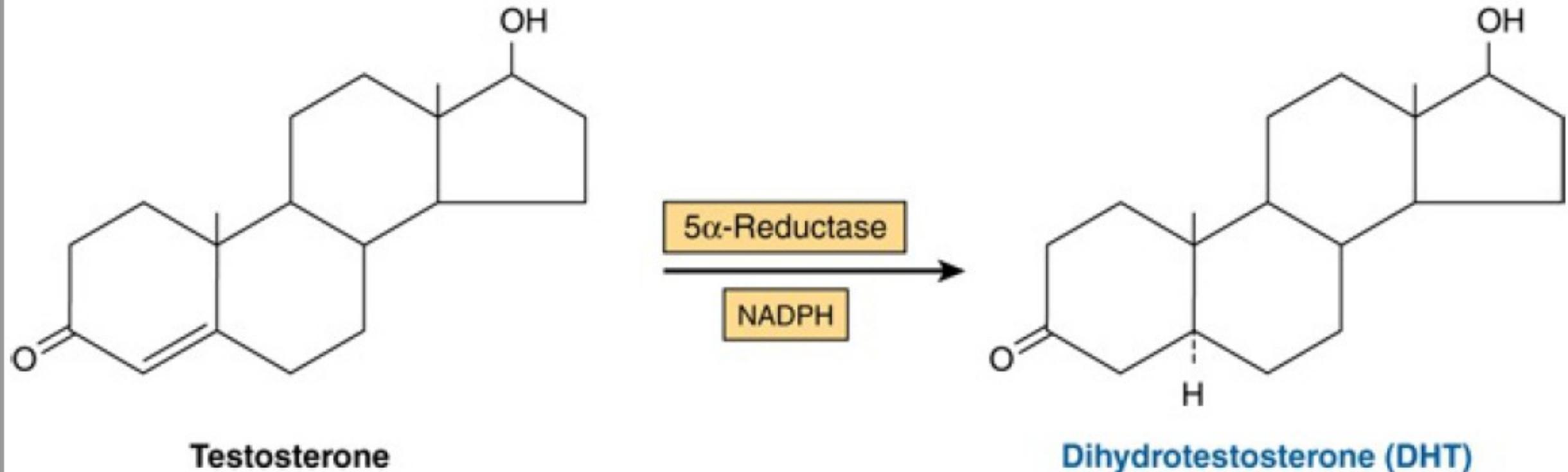
A. In males: testes produce spermatozoa and testosterone.

B. In females: Ovaries produce ova and the steroid hormones (estrogens and progesterone).

Testicular steroidogenesis: Synthesis of testosterone by the Leydig cells of the human testicle

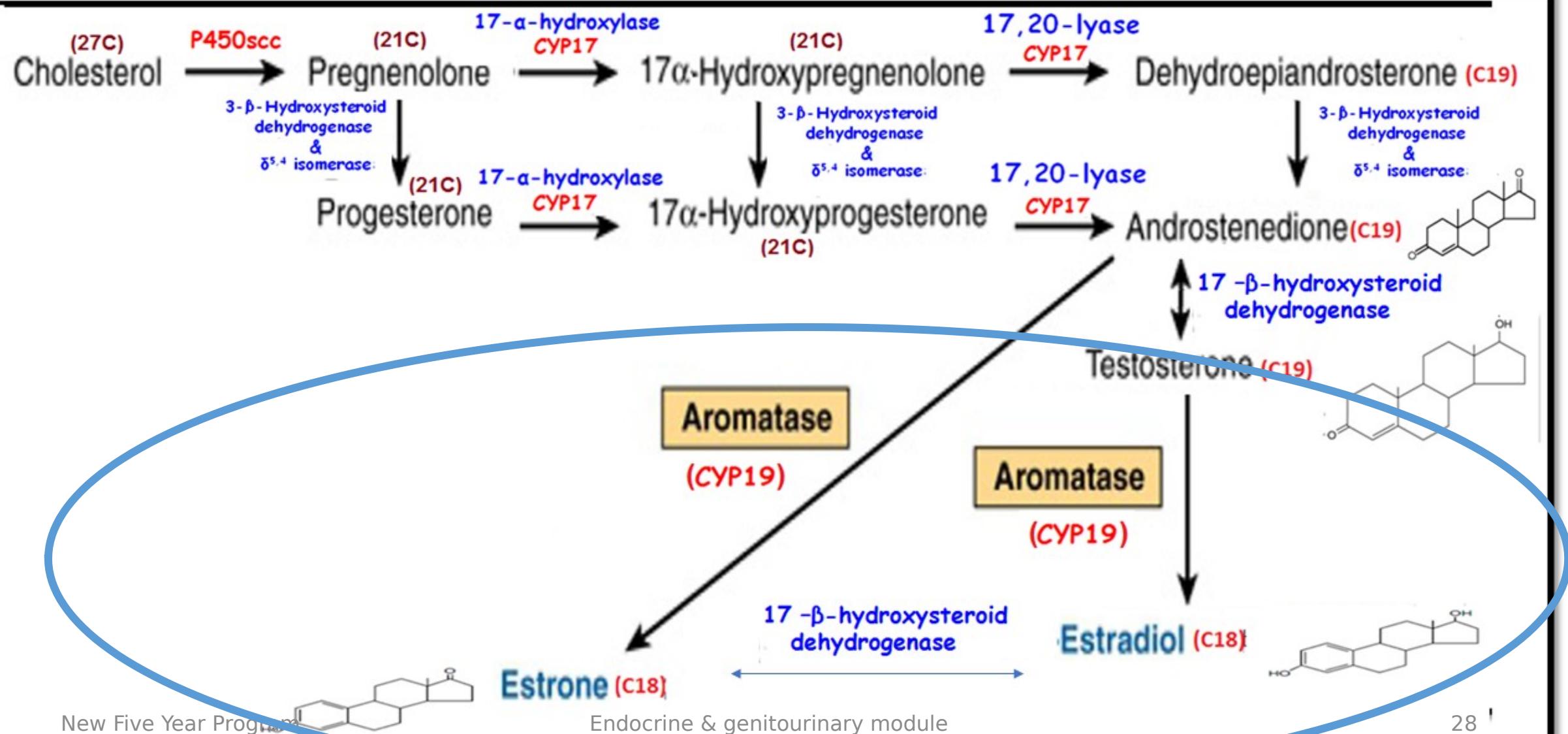


In its target cells the double bond in ring A of testosterone is reduced through the action of **5 α -reductase** enzyme, forming the more potent androgen **dihydrotestosterone (DHT)**



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry*, 29th Edition: www.accessmedicine.com

Ovarian steroidogenesis



Ovarian steroidogenesis



- Estrogens are derived from androgens (testosterone & androstenedione) by **aromatase enzyme** (CYP19).
 - **Theca cells** are the source of testosterone & androstenedione. These androgens are converted by the **aromatase** enzyme in **granulosa cells** to estradiol (E2) & estrone (E1) respectively.
 - **Estradiol**, the predominant and most potent of the ovarian estrogens.

Ovarian steroidogenesis



- Aromatase enzyme (**CYP19**), a member of the cytochrome P450 superfamily.
 - The **aromatase** enzyme can be found in **many tissues** including **granulosa** cells, **adipose** cells, **liver**, **skin** & other tissues.
 - In obese men, overproduction of estrogen in fat cells can cause **gynecomastia** = excessive male breast development.
 - Aromatase inhibitors are used in the treatment of estrogen-responsive breast cancer in postmenopausal women.



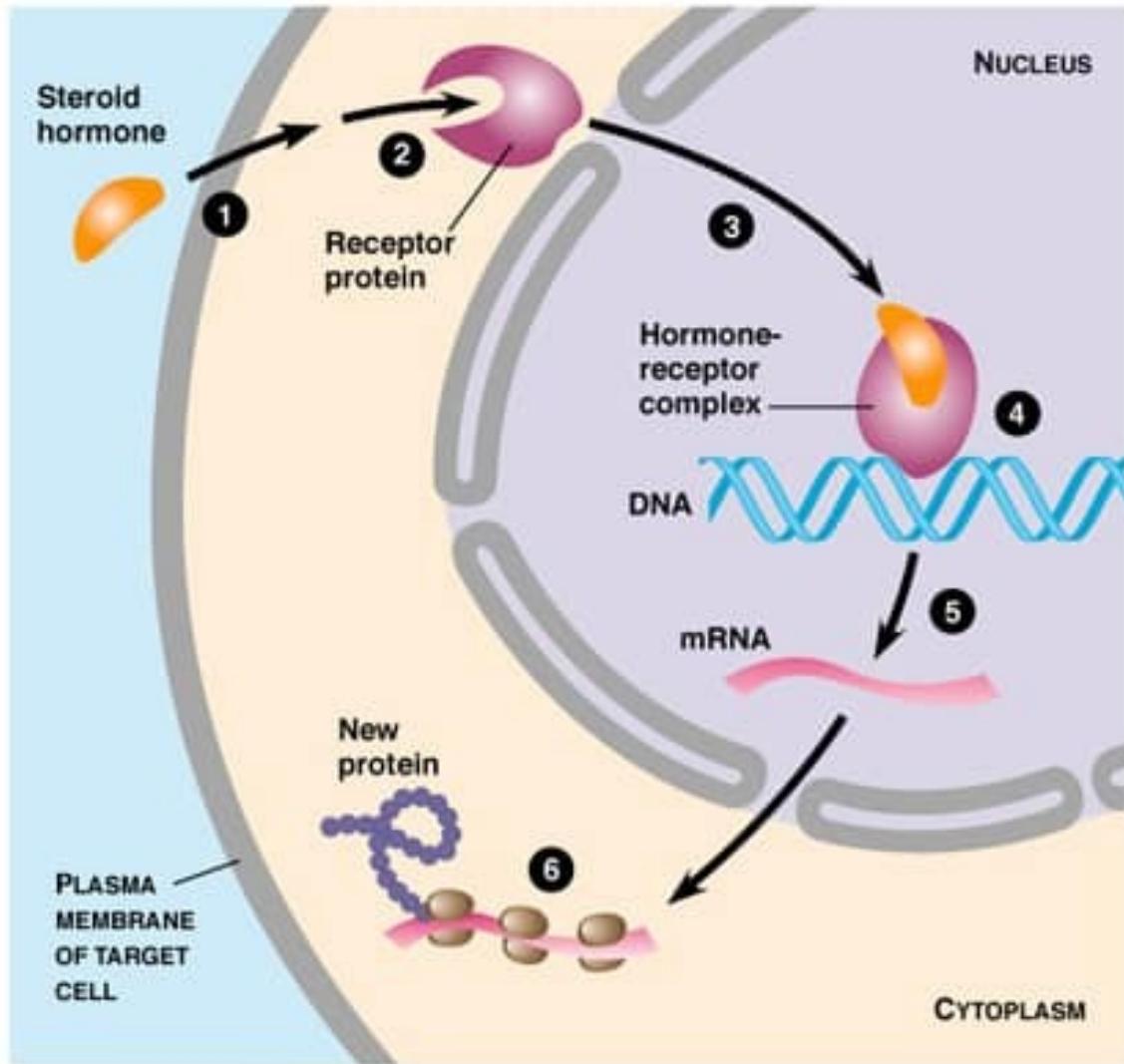
Note: All Enzymes involved in Steroid hormones are present in the **SER** except {**P450scc, Aldosterone synthase & 11- β -hydroxylase**} are **mitochondrial** enzymes.

- Steroidogenesis thus involves the repeated **shuttling** of substrates **into** and **out of** the **mitochondria**.

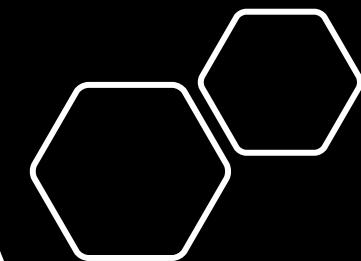


Quiz

- The enzyme catalyzing conversion of androstenedione to testosterone is a
 - (A) Oxygenase (B) Dehydrogenase
 - (C) Isomerase (D) Decarboxylase
- Conversion of testosterone to estradiol requires the enzyme:
 - (A) Aromatase (B) Dehydrogenase
 - (C) Lyase (D) Isomerase



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Mechanism of steroid hormone action

New Five-Year Program



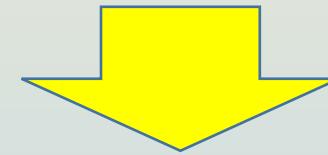
- Because of their **hydrophobicity**,
- they must be complexed with a plasma protein:

1- Plasma **albumin** can act as a **nonspecific** carrier.

2- **Specific steroid-carrier** plasma proteins:



Corticosteroid-binding globulin (transcortin) is responsible for transporting cortisol

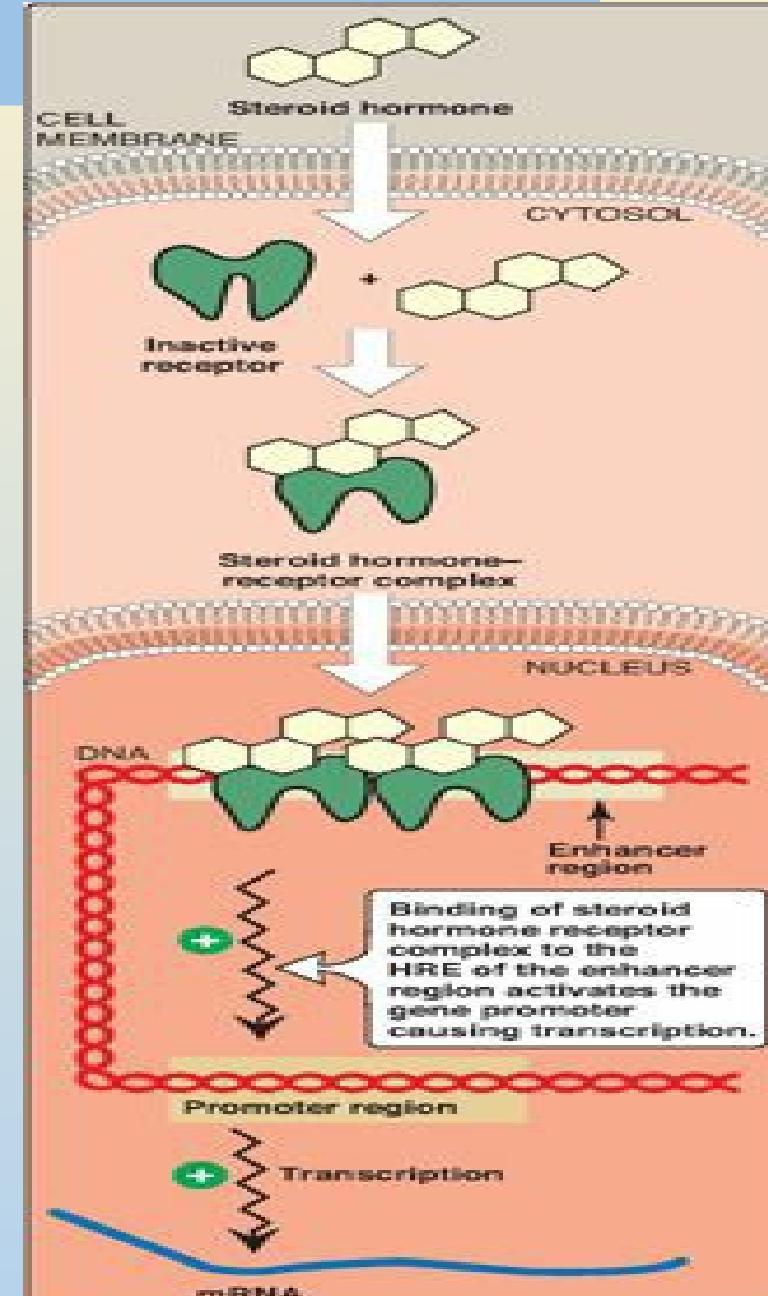


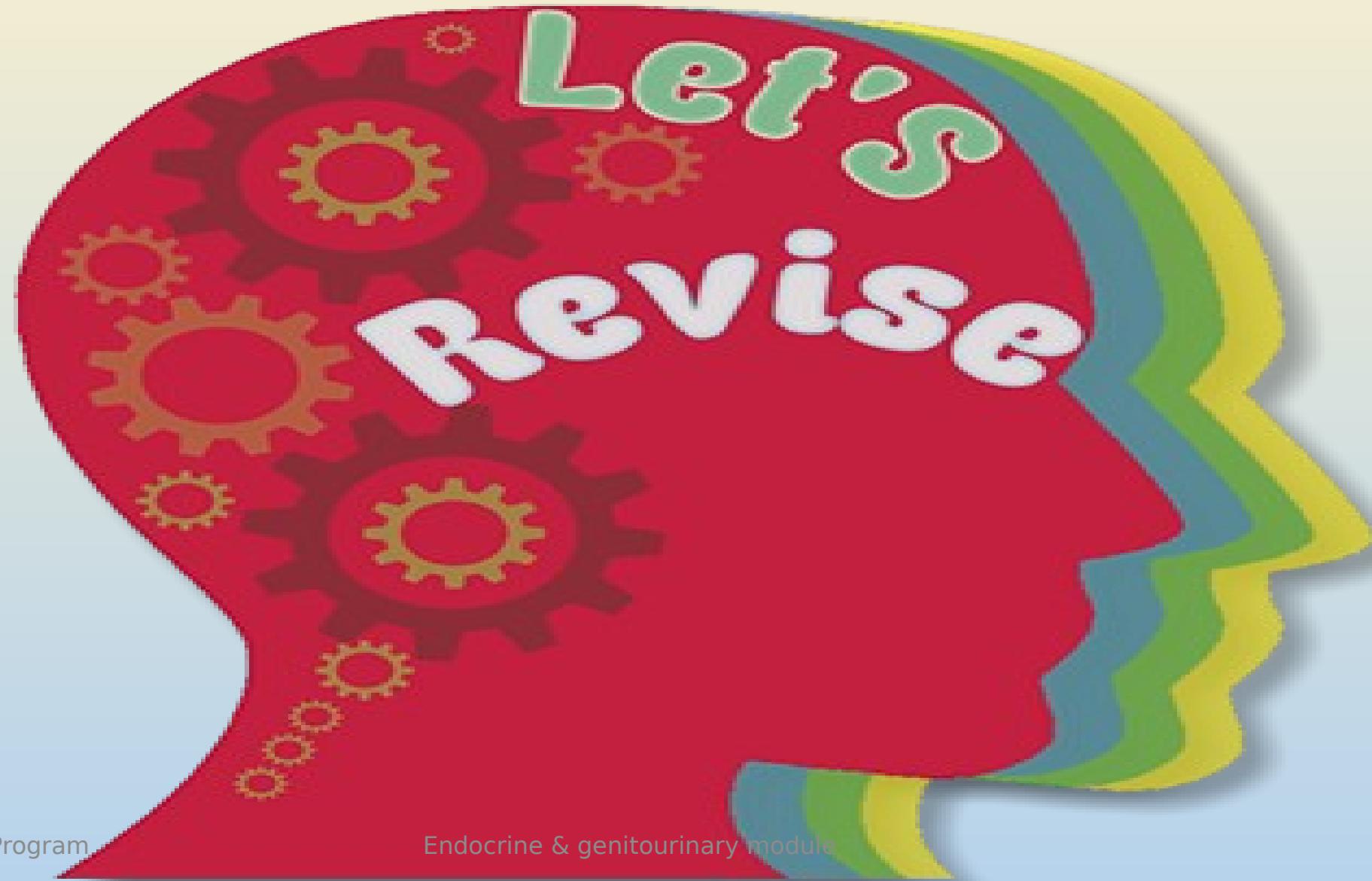
Sex hormone-binding globulin that transports sex hormones: **testosterone** and **estrogens**

1. Cortisol circulates In plasma In free form (8%) and in association of protein (92%).
2. The free cortisol Is the biologically active form of the hormone.

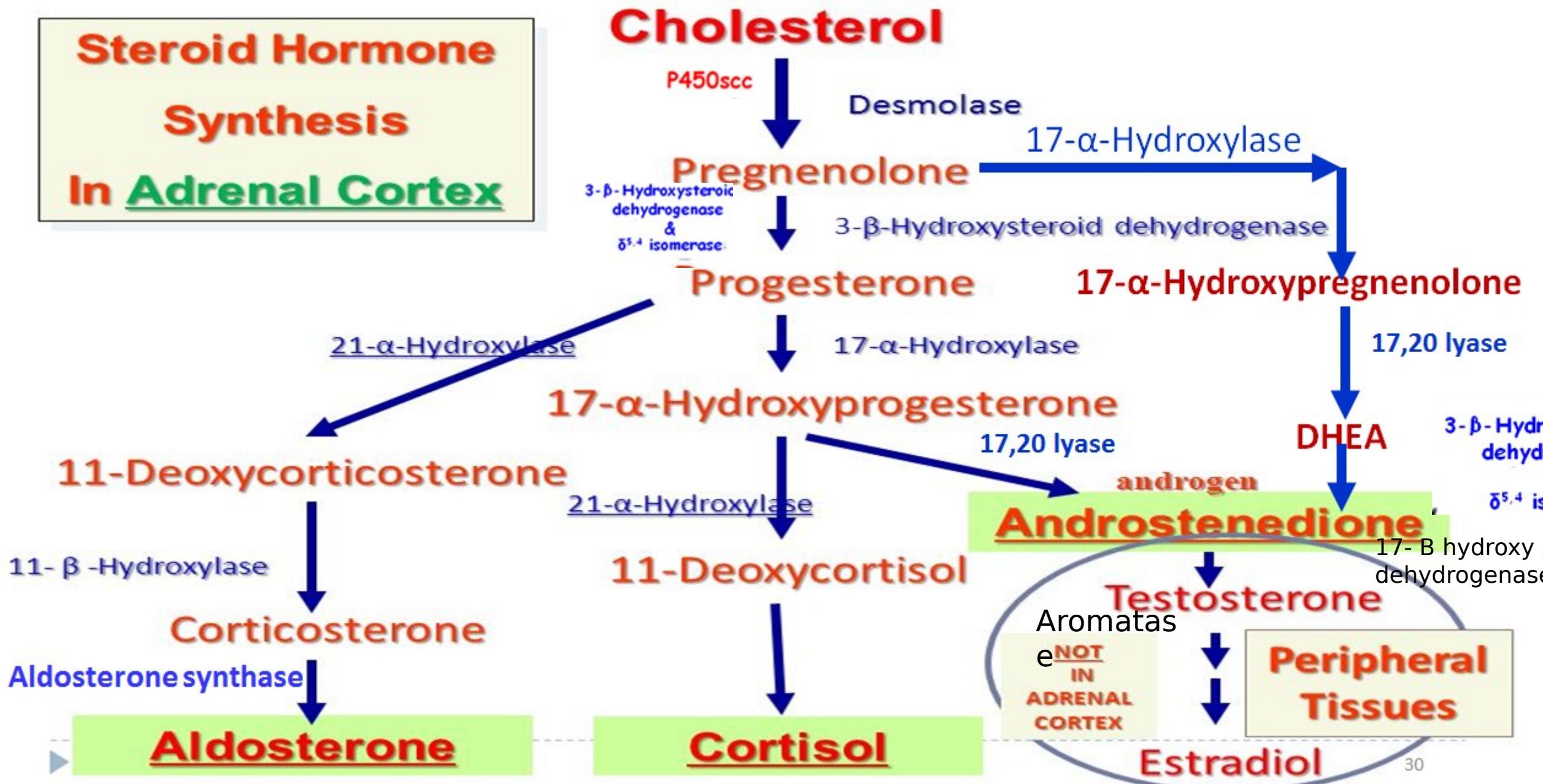
Mechanism of steroid hormone action {Hormones Group:I}

- Steroid hormones can cross the plasma membrane of its target cell and binds to a specific **cytosolic receptor**. These receptor-ligand complexes accumulate in the nucleus, dimerize, and bind to specific regulatory DNA sequences **[HREs]**
- HRE in association with coactivator or corepressors
- So, HREs can inhibit or activate transcription Of the appropriate gene sequences on the DNA.





Steroid Hormone Synthesis In Adrenal Cortex





Clinical importance

- 1-Congenital adrenal hyperplasias (CAH)**
- 2-Polycystic ovary syndrome**



Case Scenario

- A 5 year old boy was admitted to the clinic, complaining of severe **dizziness**.
- The boy was **hypotensive**
- On examination, the boy showed signs of **premature puberty** (**hirsutism, enlargement of genitalia, and muscular development**).





Case Scenario

- **Laboratory investigations showed:**
 - low serum aldosterone and cortisol levels, hyponatremia, hyperkalemia , and hypoglycemia.
 - Enzymatic assay of **21- α -Hydroxylase enzyme**, showed deficiency of the enzyme.
 - The boy was diagnosed as **congenital adrenal hyperplasia**, and was treated accordingly.



CONGENITAL ADRENAL HYPERPLASIA



Congenital adrenal hyperplasias (CAH)

Describes a group of inherited disorders characterized by **enzyme defects in the **steroidogenic** pathways involved in the **biosynthesis of steroid hormones****

(Any of several **autosomal recessive** diseases resulting from **mutations of genes for enzymes** mediating the biochemical steps of production of **mineralocorticoids, glucocorticoids or sex steroids** from cholesterol by the **adrenal glands**)

CONGENITAL ADRENAL HYPERPLASIAS (CAH)

3- β -HYDROXYSTEROID DEHYDROGENASE DEFICIENCY

- Virtually no glucocorticoids, mineralocorticoids, active androgens, or estrogens
- Salt excretion in urine
- Female-like genitalia
- Autosomal recessive with incidence of 1:10,000

17- α -HYDROXYLASE DEFICIENCY

- Virtually no sex hormones or cortisol
- Increased production of mineralocorticoids causing sodium and fluid retention and, therefore, hypertension
- Female-like genitalia

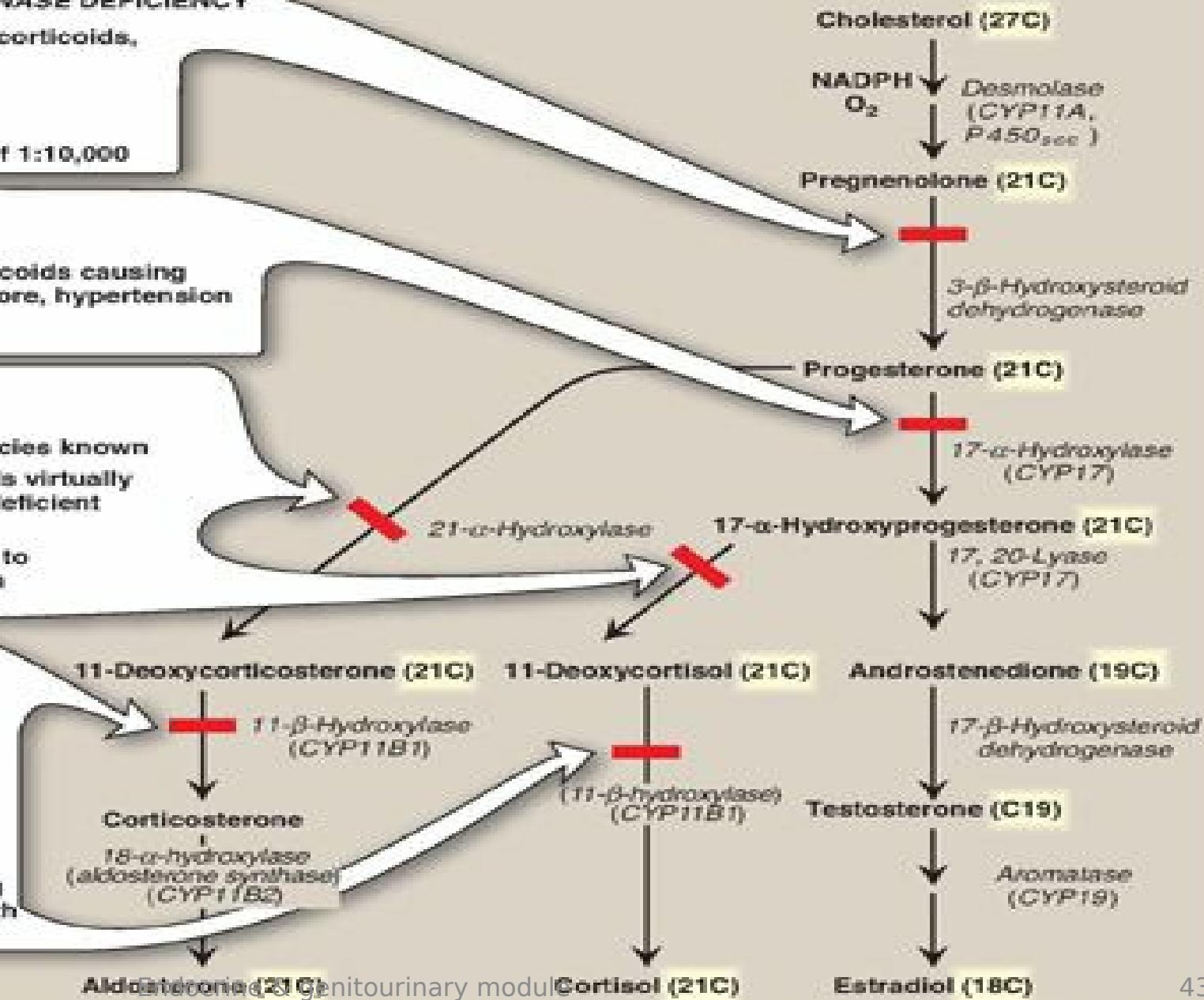
21- α -HYDROXYLASE DEFICIENCY

- Most common form of CAH (>90%)
- Partial and virtually complete deficiencies known
- Mineralocorticoids and glucocorticoids virtually absent (salt wasting classic form) or deficient (nonclassic form)
- Overproduction of androgens leading to masculinization of external genitalia in females and early virilization in males

11- β -HYDROXYLASE DEFICIENCY

- Decrease in serum cortisol, aldosterone, and corticosterone
- Increased production of deoxycorticosterone causes fluid retention (because this hormone suppresses the renin-angiotensin system, it causes low-renin hypertension)
- Overproduction of androgens causing masculinization and virilization (as with 21- α -hydroxylase deficiency)

STEROID HORMONE SYNTHESIS

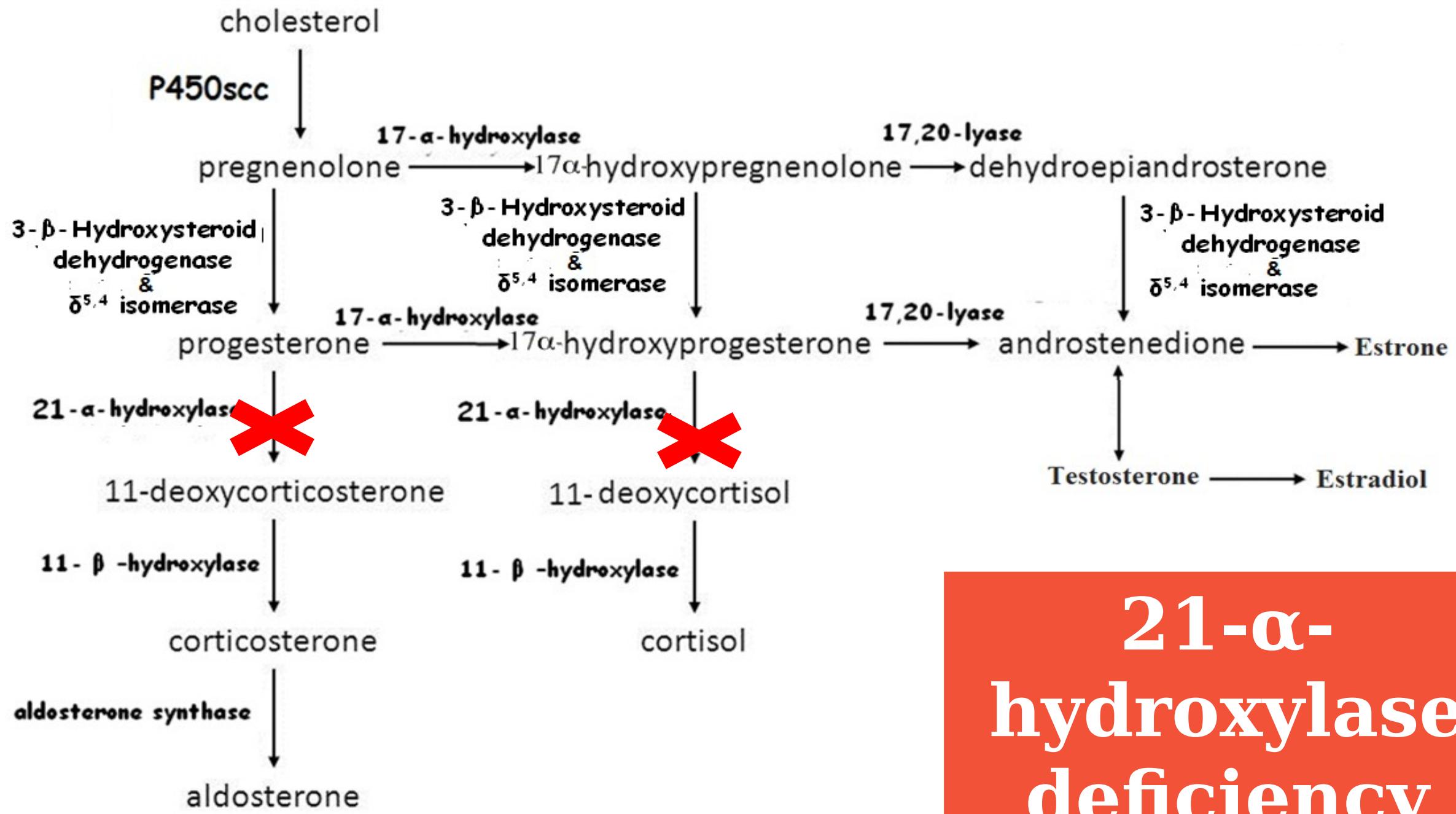


Congenital adrenal hyperplasias (CAH)

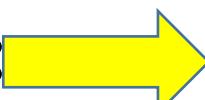


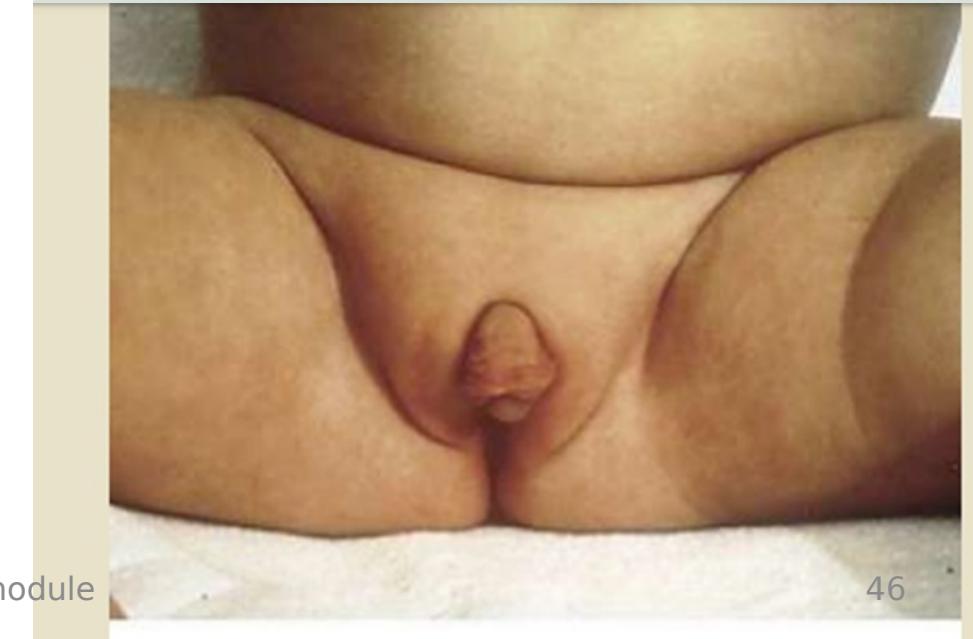
5 major Enzymes deficiency are clinically important:

- 21- α -Hydroxylase deficiency
- 11- β -Hydroxylase deficiency
- 17- α -Hydroxylase deficiency
- 3- β -Hydroxysteroid dehydrogenase deficiency
- 20,22 Desmolase deficiency



21- α -hydroxylase deficiency

- Most common form of CAH (**>90%**).
- Partially and complete deficiencies are known.
- Mineralocorticoids & glucocorticoids are virtually absent (**salt wasting classic form**) or deficient (**non classic form**).
- Overproduction of adrenal androgens:  prenatal masculinization of female genitalia (**ambiguous genitalia**) & early **virilization of males**.



21- α -hydroxylase deficiency

Salt wasting classic form:

- Hypotension, Hyponatremia, Hyperkalemia.
- Failure to thrive, recurrent vomiting, dehydration, and shock.



◦ **B:** Boy with salt-losing CAH present at 7–10 days of age with a salt-losing adrenal crisis with **hyperpigmentation** on physical examination (note **scrotal hyperpigmentation**).



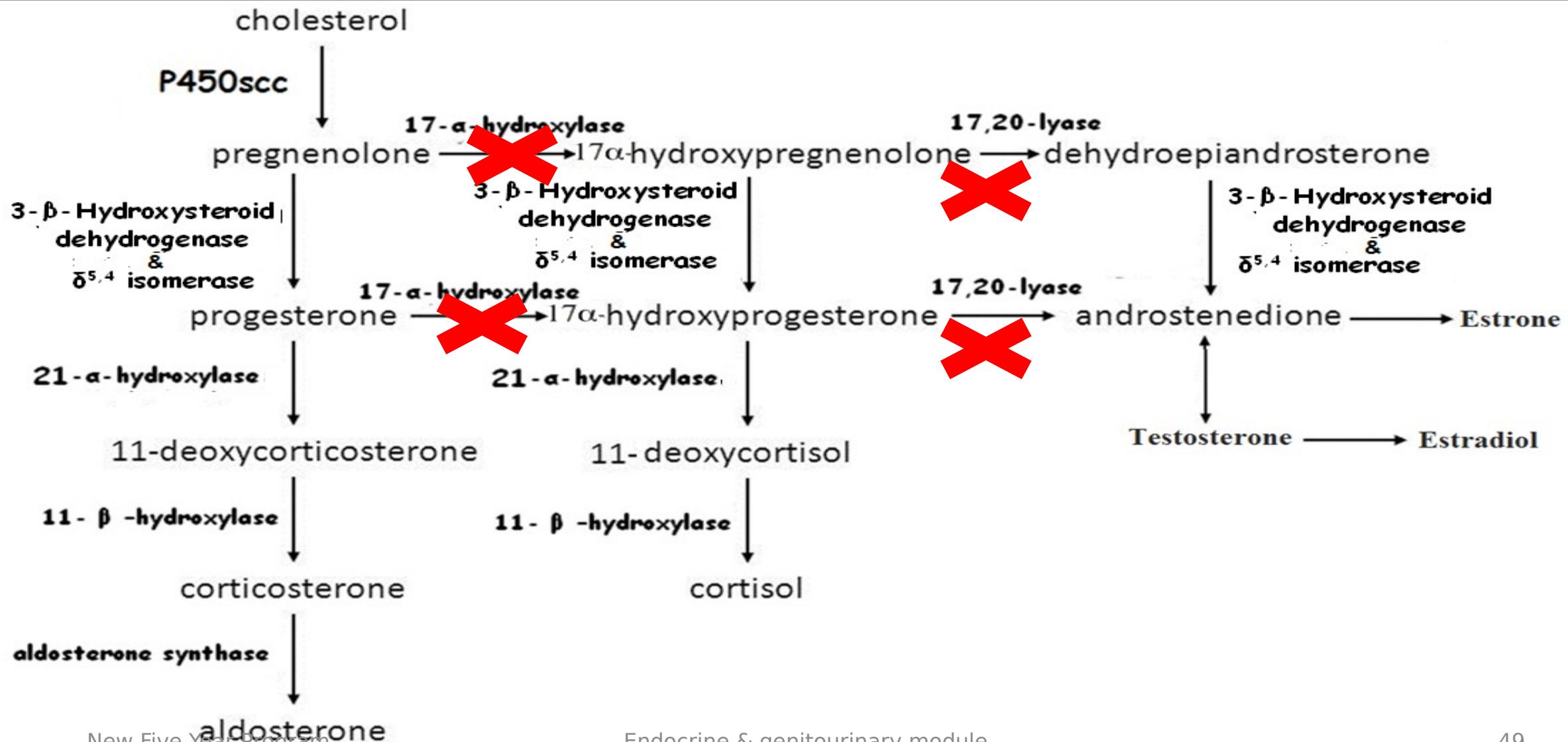
21- α -hydroxylase deficiency

Treatment:

1. Treatment is life-long
2. Steroid replacement
3. Plastic surgery for ambiguous genitalia at early age
4. Genetic counseling
5. Psychological support



17- α -hydroxylase deficiency



17- α -hydroxylase deficiency



- Cortisol & sex hormones deficiency
- Increased production of mineralocorticoids (aldosterone)
hypertension
- Female like genitalia in males at birth



What is polycystic ovary syndrome?

Stein-Leventhal syndrome

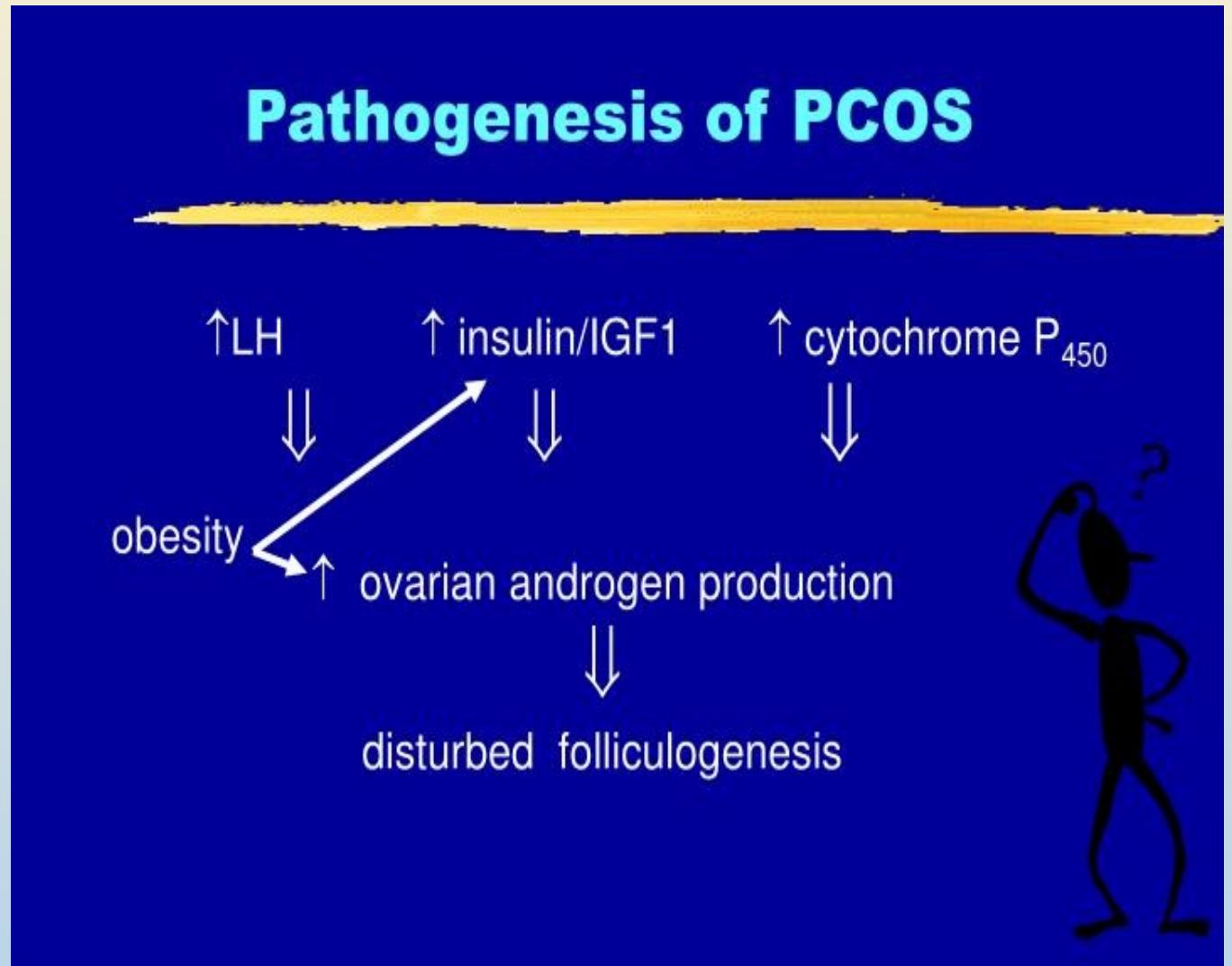
- **Most common gynaecological condition** affecting women of childbearing age
- Also associated with the **Metabolic syndrome**
- **syndrome of ovarian hyperandrogenisation**
- **associated symptoms of Androgen excess**
- **Anovulation** leads to menstrual irregularity



Stein-leventhal syndrome

Polycystic ovary syndrome (PCOS) is a condition that affects a woman's hormone levels.

Women with PCOS produce higher-than-normal amounts of male hormones.
This hormone imbalance causes them to skip menstrual periods and makes it harder for them to get pregnant.



PCOS SYMPTOMS



HAIR LOSS HIRSUTISM PELVIC PAIN

INFERTILITY OVERWEIGHT MONTH

FATIGUE HIGH TESTOSTERONE LEVELS ACNE

POLYCYSTIC OVARY SYNDROMES (PCOS)



Biochemistry in PCOS

- ❖ **Raised LH or LH:FSH ratio**
- **One or more androgen levels (raised testosterone/ androstendione / DHEAS)**
- ❖ **PCOS is also associated with a characteristic metabolic syndrome that includes:**
 - insulin resistance • dyslipidemia • hypertension
 - These features are linked with increased risks of type 2 diabetes and possibility of premature cardiovascular disease





The most common form of Congenital Adrenal Hyperplasia (CAH) results from a deficiency of which of the following?

1. 11- β -hydroxylase
2. 17-OH progesterone
3. 17- α - hydroxylase
4. 21-hydroxylase

SUGGESTED TEXTBOOKS



1. Lippincott's Illustrated Reviews in Biochemistry



Thank You

Marwa Dahpy